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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,959	06/25/2001	Richard Ian Christopherson	DAVI139.001C1	2583

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/888,959	CHRISTOFERSON ET AL	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,18-21 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 2, 18-21 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 9, 2007 has been entered.

Claim 1 has been amended. Claims 24-27 have been added. Claims 1, 2, 18-21 and 24-27 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 18-21 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites an array comprising from 20 to about 1000 regions, wherein each region comprises immunoglobulins specific for a distinct cell surface marker antigen and where the cell surface marker antigens are selected from Table 4. Table 4 contains only 47 antibodies to distinct marker antigens. It is unclear how 953 other distinct cell surface antigens can be accommodated being confined to the surface marker antigens of Table 4. It appears that the array can consist of antibodies which are not limited to the antibodies of the Table 4. Further, because of this ambiguity, it is unclear if the array must embody all of the antibodies of Table 4, or a single antibody selected from Table 4. For purpose of examination, all alternative will be considered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 18-21, 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to new matter

Claim 1 has been amended to recite the limitation" wherein the array comprises from 20 to about 1000 regions". The limitation is not supported by the originally filed disclosure which states that the preferred number of regions (spots) is from 7 to 1000, or from about 10 to 1000 (page 35, lines 15-18). This fails to provide support for the new range of 20 to about 1000.

(B)As drawn to inadequate written description

The instant method claims encompass an array of immunoglobulin molecules of greater than 40 regions, wherein each region comprises immunoglobulins which are specific for a cell surface marker, wherein binding to cell surface antigens provides a pattern of expression on leukocytes that distinguishes leukemias of T cell, B cell or myeloid lineage. The specification provides Table 4 which comprises 47 cell surface markers in addition to four isotype control markers. The prior art teaches about 35 cell surface markers for distinguishing B, T and myeloid leukemias (Stewart et al, Cytometry, 1997, Vol. 30, pp. 231-235). The genus relied upon for the method encompasses immunoglobulins which bind to markers which are not described by the specification, or known in the prior art. The description of some 47 markers does not adequately describe the genus of cell surface markers useful for distinguishing T, B and myeloid leukemias because one cannot use the structure and function of the known markers to anticipate other, undescribed and/or unknown markers. One of skill in the art would reasonably conclude that applicant was not in possession of arrays comprising antibodies to cell surface markers beyond those described in the instant Table 4, and therefore was not in possession of the claimed method reliant on said undescribed markers.

Claims 1, 2, 18-21 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a leukemia, does not reasonably provide enablement for a method for identifying the propensity of developing a leukemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The art recognizes that leukemia is a clonal disease arising from a single cell (Mauro et al, Curr Opin Oncol. 2001, Vol. 13, pp. 3-7). The art teaches that autosomal folate-sensitive fragile sites in chromosomes may increase the risk for haematologic malignancies through a complex mechanism which remains to be clarified (abstract of Kolialexi et al, Anticancer Res. 1998 Jul-Aug;, Vol. 18, pp. 2359-2364). However, neither the specification nor the art provides an immunophenotype consistent with the propensity for developing leukemia or the pre-leukemic state. The abstract of Dorak et al (Leukemia and Lymphoma, 1994, Vol. 12, pp. 211-222) teaches that out of 112 patient with CML, those who developed the disease when aged less than 35 years (early-onset group) had higher homozygosity rates for the DOA1, HSP70 and C4 alleles of the DR53 group of ancestral haplotypes, for a subtype of HLA-A3, and a higher allele frequency of BfFb compared to the late-onset group. The oldest patient ($n = 13$) homozygous for DR53 was 52-years-old ($p = 0.004$), and all HLA-A3 homozygous patients ($n = 4$) were in the early-onset group ($p = 0.01$). The relative risk for early-onset CML yielded by HLA-A3 homozygosity was 17.6 and the HLA-identical sibling frequency was increased only in the early-onset group ($p < 0.01$). Bortin et al (Blood, 1987, Vol. 70, pp. 227-232) teaches that the frequency of Cw4 was elevated in patients with acute lymphoblastic leukemia (relative risk = 2.01, P less than 0.0003), acute myelogenous leukemia (relative risk = 2.06, P less than 0.0002), and chronic myelogenous leukemia (relative risk = 2.14, P less than 0.0008) and suggests that Cw3 and Cw4 may be markers for leukemia susceptibility. Thus, although homozygosity for DR53 is associated with earlier onset of CML, and the presence of Cw3 and Cw4 may indicate a greater susceptibility to leukemia in general, there are no teaching enabling one of skill in the art to predict when the (9:22) translocation will occur in any patient. Further Haas et al (Nature. 1992, Vol. 359, pp. 414-416) teach that in individuals harboring the (9:22) translocation, the translocated chromosome 9 was of paternal origin, whereas the translocated chromosomes 22

were derived exclusively from the maternal copy, in 11 cases with reliable polymorphisms and that this provided evidence that imprinting phenomena may play an important role in acquired tumour-specific chromosome rearrangements. Thus, the factors governing the predisposition to a (9:22) translocation and the onset of leukemia are complex, and cannot be accounted for simply by the inheritance of a mutant gene. Further there is no knowledge of the immunophenotype consistent with a preleukemic state or for differentiating between the propensity of developing a T cell, B cell or myeloid leukmia. Given the lack of teachings in the specification regarding the immunophenotypes consistent with propensity to develop T cell, B cell or myeloid leukemias, one of skill in the art would be subject to undue experimentation in order to carry out the instant method as it pertains to identifying a propensity of developing a leukemia of T cell, B cell or myeloid leukmia.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for biological samples which are blood, bone marrow, CSF and lymph, does not reasonably provide enablement for biological samples which are "tissue fluid", seminal fluid and mucus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claim requires that specimens such as "tissue fluid", seminal fluid and mucus be used to distinguish between leukemias of T cell, B cell or myeloid lineage. The art teaches the diagnostic utility of immunophenotyping using blood, lymph or CSF in the management of leukemia (for example, abstract of Wang et al, Am J Hematology, 1995, Vol. 50, pp. 188-199). Neither the specification nor any art of record has provided objective evidence that representative cells of T lineage, B lineage or myeloid leukemias are present in tissue fluids, seminal fluid and mucus or present the extent that said cells can be a reliable indicator of leukemia relative to a normal individual. It is further notes that "tissue fluid" encompasses the fluid from any tissue sample taken from an individual, and mucus encompasses any mucus taken from any body cavity of an individual, such as cervical, bronchial or nasal. Given the lack of teachings in the specification or any art of record regarding the diagnostic utility of the broadly claimed "tissue fluids" seminal fluids and mucus in the discernment of different types of

leukemias, one of skill in the art would be subject to undue experimentation in order to carry out the broadly claimed method.

Claims 1, 2, 19, 20, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanza et al (European Journal of Histochemistry, 1996, Vol. 40 suppl. 1, pp. 7-14) in view of Chang (Journal of Immunological Methods, 1983, Vol. 65, pp. 217-233, reference of the IDS filed April 29, 2003) and Ruiz-Arguelles et al (Cytometry, 1998, vol. 34, pp. 39-42)..

Claim 1 is drawn in part to a method for identifying a leukemia of a T-cell, B-cell or myeloid cell lineage in a subject comprising contacting a biological sample comprising leukocytes from the human subject with an array of immunoglobulin molecules immobilized to a solid support, wherein the array comprises from 20 to about 1000 regions, wherein each region comprises immunoglobulin molecules that are specific for a distinct surface marker antigen, wherein the binding of the immunoglobulin molecules to the distinct cell surface marker antigens provides a pattern of expression of the leukocytes that distinguishes leukemias of T cell, B cell or myeloid lineage, wherein the cell surface marker antigen are selected from Table 4 such that the patterns of expression of the cell surface antigen on the leukocytes distinguish leukemias of T cell, b cell or myeloid lineage; and determining the relative scale of the pattern of expression with which cell surface marker antigens have bound to which immobilized immunoglobulin molecule to establish a differential pattern of density of binding that identifies a leukemia cell that is of T cell, B cell or myeloid lineage. claim 2 embodies the method of claim 1 wherein the immunoglobulin molecules are monoclonal antibodies. Claims 19 and 20 embody the method of claim 1 wherein the biological sample is blood. . Claim 26 embodies the method of claim 1 further comprising microscopic analysis of cellular morphology of the leukocytes.

Lanza et al disclose a flow cytometric method for identifying a leukemic of a T-cell, B-cell or myeloid cell lineage (page 11, Table IV) comprising 27 of the antibodies listed in the instant table 4. Lanza et al teach that a problem with flow cytometry is that the operator must choose a threshold for positivity, and that this threshold is subjective leading to false positive or false negative results (page 12, first column, second full paragraph). Lanza et al do not teach the use of an antibody array comprising the antibodies used in the flow cytometric determination.

Ruiz-Arguelles et al teach the flow cytometric immunophenotyping of leukemia cells and specifically teach that the relative intensity of a given antigen can be different from normal and thus classified by dim or bright relative to normal.

Chang teaches binding of cells to matrixes of distinct antibodies coated on solid surfaces. Chang teaches that such a matrix can be used to analyze functionally different cell subpopulations tat express distinct differentiation antigens (page 222, lines 15-18 under the heading of "Discussion"). Chang suggest that the antibody matrix method can be used to determine the proportion of specific subsets in a mixed population, such as the proportions of B-cells, T cells and monocytes in the mononuclear cell fraction (page 223, lines 2-5). Chang et al teach the evaluation of cell binding to the antibody "dots" by means of microscopic examination (page 219, lines 16-17 under the heading "Binding of cells to small areas of antibody-coated surface"), which fulfills the specific embodiment of claim 26 requiring microscopic analysis. Chang teaches that no fluorescent staining was included (page 219, last sentence under the heading "Evaluation of cell binding") and that it allows for exposure to the sample to all the antibodies at discrete location at the same time and thereby saves reagents and saves cell samples (page 222, first paragraph under "Discussion").

It would have been prima facie obvious at the time the claimed invention was made to use all the monoclonal antibodies in a antibody matrix in order to differentiate between T cell, B-cell and myeloid leukemia. One of skill in the art would have been motivated to do so by the teachings of Chang on saving time and cellular samples by exposing the cell sample to all of the antibodies by means of the matrix at the same time. Further one of skill in the art would have been motivated to dilute the sample such that not all of the antibody dots were filled to capacity as indicated by Chang. By doing so it would allow for the relative assessment of cell binding relative to a normal cell sample and thus replace the classification of dim or bright as assess by flow cytometry, taught by Ruiz-Arguelles et al , with the actual number of cells adhering to the dot in comparison to the actual number of cells adhering to the dot using a normal sample. This would allow for a comparison to the normal sample to be made which would reflect actually relative differences between antigen expression in the patient sample and the normal sample which can then be construed as relative differences between the phenotype of T-cell leukmia, B-cell leukemia and myeloid cell leukemia. One would also have been motivate to use the method

of Chang because it avoid the requirement for fluorescence markers which is part of flow cytometric analysis and therefore reduces the cost of the analysis.

Claims 1, 2, 19, 20, 24, 26, 27 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanza et al in view of Chang and Ruiz-Arguelles et al as applied to claims 1, 2, 19, 20, 26 and 27 above, and further in view of Stewart et al (Cytometry, 1997, Vol. 30, pp. 231-235).

Claim 24 embodies the method of claim 1 wherein the array of immunoglobulins comprises at least 40 discrete regions, wherein each region comprises immunoglobulins that are specific for a distinct cell, surface marker antigen. Claim 27 embodies the method of claim 1 further comprising histochemical. biochemical or immunological analysis of the leukocytes.

Stewart et al teach that the larger the number of reagents the higher the sensitivity of abnormal cell detection and the better the ability of delineating phenotypes useful in disease monitoring (page 233, first column, lines 2-6) Stewart et al teach that a limited panel would limit the ability of detecting minimal neoplastic involvement (page 234, second column, lines 18-23). Stewart et al teach an additional eight more antibodies from the list in the instant Table 4 (Table 1 and Table 4). Stewart et al teach uptake of a dye to indicate dead cells which bind to antibodies (page 233, second column, paragraph number 3) which fulfills the specific requirement of claim 27 requiring biochemical analysis of the leukocytes.

It would have been prima facie obvious at the time the claimed invention was made to use the border set of antibodies taught by Stewart et al and to exposure the cells bound to the matrix to dye-exclusion test. One of skill in the art would have been motivated to do so by the teachings of Stewart et al regarding the benefit of greater sensitivity conferred with increased numbers of reagents and the necessity of excluding dead cells from the assay.

Claims 1, 2, 18, 19, 20 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanza et al and Chang and Ruiz-Arguelles et al as applied to claims 1, 2, 19, 20, 26 and 27 above, and further in view of Paul (Fundamental Immunology, Third Edition, 1993, page 460).

Paul teaches that polyclonal antibodies have advantages over monoclonal antibodies including easier access to sera having the right range of activity without the burden of finding

the appropriate monoclonal antibody with the right range of reactivities (page 460, second column, first two paragraphs under "Polyclonal Versus Monoclonal Antibodies").

It would have been prima facie obvious at the time the claimed invention was made to use polyclonal antibodies which bind to the antigens taught by Lanza et al. One of skill in the art would have been motivated to do so by the teachings of Paul on the uses of polyclonal antibodies as alternatives to monoclaonl antibodies.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicant's amendments and arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
4/28/2007

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PRIMARY EXAMINER